

PRESCRIBING INFORMATION

Infanrix® Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed

DESCRIPTION

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is a sterile combination of diphtheria and tetanus toxoids and three pertussis antigens [inactivated pertussis toxin (PT), filamentous hemagglutinin (FHA) and pertactin (99 kilodalton outer membrane protein)] adsorbed onto aluminum hydroxide. *Infanrix* is intended for intramuscular injection only. After shaking, the vaccine is a homogeneous white turbid suspension.

Three acellular pertussis antigens (pertussis toxin [PT], filamentous hemagglutinin [FHA] and pertactin) are isolated from phase 1 *Bordetella pertussis* culture grown in modified Stainer-Scholte liquid medium. PT and FHA are extracted from the fermentation broth by adsorption on hydroxyapatite gel; pertactin is extracted from the cells by heat treatment and flocculation using barium chloride. These antigens are purified in successive chromatographic steps: PT and FHA by hydrophobic, affinity and size exclusion; pertactin by ion exchange, hydrophobic and size exclusion processes. PT is detoxified using formaldehyde and glutaraldehyde. FHA and pertactin are treated with formaldehyde.

Diphtheria toxin is produced by growing *Corynebacterium diphtheriae* in Linggoud and Fenton medium containing a bovine extract. Tetanus toxin is produced by growing *Clostridium tetani* in a modified Latham medium. Both toxins are detoxified with formaldehyde, concentrated by ultrafiltration, and purified by precipitation, sterile filtration and dialysis.

Each antigen is individually adsorbed onto aluminum hydroxide. Each 0.5 mL dose contains, by assay, not more than 0.625 mg aluminum. Each 0.5 mL dose is formulated to contain 25 LF diphtheria toxoid, 10 LF tetanus toxoid (both toxoids induce at least 2 antitoxin units/mL of serum in the guinea pig potency test), 25 mcg PT, 25 mcg FHA and 8 mcg pertactin. The potency of the pertussis component is evaluated by measurement of the antibody response to PT, FHA and pertactin in immunized mice using an ELISA.

Each 0.5 mL dose also contains 2.5 mg 2-phenoxethanol as a preservative, 4.5 mg sodium chloride, water for injection and not more than 0.02% (w/v) residual formaldehyde. Thimerosal is used in the early stages of manufacturing and is removed by subsequent purification steps to below the analytical detection limit, which calculation is <1 ng mercury/dose. Does not contain thimerosal as a preservative.

The vaccine contains polysorbate 80 [Tween 80] which is used in the production of the pertussis concentrate. The inactivated acellular pertussis components contribute less than 5 endotoxin units [EU] per 0.5 mL dose.

Diphtheria and Tetanus Toxoids adsorbed bulk concentrates for further manufacturing use are produced by Chiron Behring GmbH & Co, Marburg, Germany. The acellular pertussis antigens are manufactured by SmithKline Beecham Biologiques S.A., Rixensart, Belgium. Formulation, filling, testing, packaging and release of the vaccine are conducted by SmithKline Beecham Biologicals S.A.

CLINICAL PHARMACOLOGY

Simultaneous immunization against diphtheria, tetanus and pertussis during infancy and childhood using a conventional whole-cell DTP vaccine has been a routine practice in the United States since the late 1940s. It has played a major role in markedly reducing the incidence of, and deaths from, each of these diseases.

Diphtheria

Diphtheria is primarily a localized and generalized intoxication caused by diphtheria toxin, an extracellular protein metabolite of toxigenic strains of *Corynebacterium diphtheriae*. While the incidence of diphtheria in the United States has decreased from over 200,000 cases reported in 1921,¹ before the general use of diphtheria toxoid, to only 30 cases of respiratory diphtheria reported from 1983 to 1993,² the ratio of fatalities to attack rate has remained constant at about 5% to 10%. The highest case fatality rates are in the very young and in the elderly. Diphtheria remains a serious disease in some areas of the world as evidenced by the recent outbreak in the former Soviet Union.³ Protection against disease is due to the development of neutralizing antibodies to the diphtheria toxin. Following adequate immunization with diphtheria toxoid, it is thought that protection lasts for at least 10 years.⁴ Serum antitoxin levels of at least 0.01 antitoxin units per mL are generally regarded as protective.⁴ This significantly reduces both the risk of developing diphtheria and the severity of clinical illness. Immunization with diphtheria toxoid does not, however, eliminate carriage of *C. diphtheriae* in the pharynx or nose or on the skin.¹ Efficacy of the diphtheria toxoid used in *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) was determined on the basis of immunogenicity studies, with a comparison to a serological correlate of protection (0.01 antitoxin units/mL) established by the Panel on Review of Bacterial Vaccines and Toxoids.⁴ A Vero cell toxin neutralizing test confirmed the ability of infant sera (N=45), obtained 1 month after the primary course, to neutralize diphtheria toxin. Protective titers (≥ 0.01 antitoxin units/mL of serum) were achieved in 100% of the sera tested.

Tetanus

Tetanus is an intoxication manifested primarily by neuromuscular dysfunction caused by a potent exotoxin released by *Clostridium tetani*. The incidence of tetanus in the United States has dropped dramatically with the routine use of tetanus toxoid to a record low of 45 cases in 1992.⁵ Tetanus in the U.S. is primarily a disease of older adults. Of 99 tetanus patients with complete information reported to the Centers for Disease Control and Prevention during 1987 and 1988, 68% were ≥ 50 years of age, while only 6 were < 20 years of age. No cases of neonatal tetanus were reported. Overall, the case-fatality rate was 21%. The disease continues to occur almost exclusively among persons who are unvaccinated or inadequately vaccinated or whose vaccination histories are unknown or uncertain.⁵

Spores of *C. tetani* are ubiquitous. Serological tests indicate that naturally acquired immunity to tetanus toxin does not occur in the U.S. Thus, universal primary immunization with tetanus toxoid, with subsequent maintenance of adequate antitoxin levels by means of timed boosters, is necessary to protect all age groups.¹ Protection against disease is due to the development of neutralizing antibodies to the tetanus toxin. Tetanus toxoid is a highly effective antigen and a completed primary series generally induces serum antitoxin levels of at least 0.01 antitoxin units per mL, a level which has been reported to be protective.⁴ It is thought that protection persists for at least 10 years.⁴ Efficacy of the tetanus toxoid used in *Infanrix* was determined on the basis of immunogenicity studies with a comparison to a serological correlate of protection (0.01 antitoxin units per mL) established by the Panel on Review of Bacterial Vaccines and Toxoids.⁴ An *in vivo* mouse toxin neutralizing test confirmed the ability of infant sera (N=45), obtained 1 month after the primary course, to neutralize tetanus toxin. Protective titers (≥ 0.01 antitoxin units/mL of serum) were achieved in 100% of the sera tested.

Pertussis

Pertussis (whooping cough) is a disease of the respiratory tract caused by *Bordetella pertussis*. Pertussis is highly communicable (attack rates in unimmunized household contacts of up to 90% have been reported⁶) and can cause severe disease, particularly among the very young.⁷ Since immunization against pertussis became widespread, the number of reported cases and associated mortality in the United States have declined from an average annual incidence and mortality of 150 cases and 6 deaths per 100,000 population, respectively, in the early 1940s, to annual reported incidences of 1.6, 2.6 and 1.8 cases per 100,000 population in 1992, 1993 and 1994, respectively.^{7,8} Precise epidemiologic data do not exist, since bacteriological confirmation of pertussis can be obtained in less than half of the suspected cases. Most reported illness from *B. pertussis* occurs in infants and young children in whom complications can be severe. From 1980 to 1989, of 10,749 pertussis cases reported nationally in infants less than 1 year of age, 89% were hospitalized, 22% had pneumonia, 3.0% had seizures, 0.9% had encephalopathy and 0.6% died.⁸ Older children and adults, in whom classic signs are often absent, may go undiagnosed and may serve as reservoirs of disease.⁹

Routine vaccination with whole-cell DTP vaccine has significantly reduced pertussis-related morbidity and mortality. However, concerns regarding reactogenicity of whole-cell DTP vaccine have spurred development of safer pertussis vaccines with high efficacy. The role of the different components produced by *B. pertussis* in either the pathogenesis of, or the immunity to, pertussis is not well understood.

Antigenic components of *B. pertussis* believed to contribute to protective immunity include: pertussis toxin; filamentous hemagglutinin; and pertactin.^{10,11} Although the role of these antigens in providing protective immunity in humans is not well understood, clinical trials which evaluated candidate acellular DTP vaccines manufactured by SmithKline Beecham Biologicals supported the efficacy of three-component *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed).^{12,14}

Infanrix, which contains three pertussis antigens (PT, FHA and pertactin), has been shown to be effective in preventing WHO-defined pertussis in two published clinical trials when administered as a primary series.^{13,14}

A double-blind, randomized, placebo-controlled (DT) trial conducted in Italy, sponsored by the National Institutes of Health (NIH), assessed the absolute protective efficacy of *Infanrix* when administered at 2, 4 and 6 months of age.¹³ A total of 15,601 infants were immunized with one of two tri-component acellular DTP vaccines (containing

inactivated PT, FHA and pertactin), or with a U.S.-licensed whole-cell DTP vaccine manufactured by Connaught Laboratories, Inc., or with DT vaccine alone. The mean length of follow-up was 17 months, beginning 30 days after the third dose of vaccine. The population used in the primary analysis of vaccine efficacy included 4,491 *Infanrix* vaccinees, 4,348 whole-cell DTP vaccinees and 1,470 DT vaccinees. After three doses, the protective efficacy of *Infanrix* against WHO-defined typical pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing) was 84% (95% CI: 76% to 89%) while the efficacy of the whole-cell DTP vaccine was 36% (95% CI: 14% to 52%). When the definition of pertussis was expanded to include clinically milder disease with respect to type and duration of cough, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* was calculated to be 71% (95% CI: 60% to 78%) against > 7 days of any cough and 73% (95% CI: 63% to 80%) against ≥ 14 days of any cough. A longer follow-up of the Italian trial showed that after three doses, the absolute efficacy of *Infanrix* remained high against WHO-defined pertussis at 78% (95% CI: 62% to 87%) in children whose average age was then 33 months (20-39 months).¹⁵

A prospective, blinded efficacy trial was also conducted in Germany employing a household contact study design.¹⁴ In preparation for this study, three doses of *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) were administered at 3, 4 and 5 months of age to more than 22,000 children living in six areas of Germany in a large safety and immunogenicity trial. Infants who did not participate in this trial could have received whole-cell DTP vaccine (manufactured by Behringwerke A.G., Germany) or DT vaccine. Pediatricians were asked to monitor households with a first potential case (index case) of typical pertussis which was identified by spontaneous presentation to a physician. Households were enrolled in the study if there was at least one other household member (a household contact) 6 to 47 months of age. Prospective follow-up of household contacts of index cases for the incidence and progression of pertussis was performed by a separate physician who was blinded to the vaccination status of the household. Calculation of vaccine efficacy was based on attack rates of pertussis in household contacts classified by vaccination status. Of the 173 unvaccinated household contacts, 96 developed WHO-defined pertussis (21 days or more of paroxysmal cough with infection confirmed by culture and/or serologic testing), as compared to 7 of 112 contacts vaccinated with *Infanrix* and 1 of 75 contacts vaccinated with whole-cell DTP vaccine. The protective efficacy of *Infanrix* was calculated to be 89% (95% CI: 77% to 95%), with no indication of waning of protection up until the time of the booster. The protective efficacy of the whole-cell DTP vaccine was calculated to be 96% (95% CI: 83% to 100%). The average age of *Infanrix* vaccinees at the time of follow-up in this trial was 13 months (range 6-25 months). When the definition of pertussis was expanded to include clinically milder disease, with infection confirmed by culture and/or serologic testing, the efficacy of *Infanrix* against ≥ 7 days of any cough was 67% (95% CI: 52% to 79%) and against ≥ 7 days of paroxysmal cough was 81% (95% CI: 68% to 89%). The corresponding efficacy rates of *Infanrix* against ≥ 14 days of any cough or paroxysmal cough were 73% (95% CI: 59% to 82%) and 84% (95% CI: 71% to 91%), respectively.

Immune Response to *Infanrix* Administered as a Three-Dose Primary Series

The immune responses to each of the three pertussis antigens contained in *Infanrix* were evaluated in sera obtained 1 month after the third dose of vaccine in each of three studies (schedule of administration: 2, 4 and 6 months of age in the Italian efficacy study and one U.S. study; 3, 4 and 5 months of age in the German efficacy study). One month after the third dose of *Infanrix*, the response rates to each pertussis antigen were similar in all three studies. Thus, although a serologic correlate of protection for pertussis has not been established, the antibody responses to these three pertussis antigens (PT, FHA and pertactin) in a U.S. population were similar to those achieved in two populations in which efficacy of *Infanrix* was demonstrated.

Immune Response to Simultaneously Administered Vaccines

In a small clinical trial in the United States, *Infanrix* was given simultaneously, at separate sites, with hepatitis B vaccine, *Haemophilus influenzae* type b vaccine (Hib) and poliovirus vaccine live oral (OPV), at 2, 4 and 6 months of age. One month after the third dose of hepatitis B vaccine given simultaneously with *Infanrix*, 100% of infants demonstrated anti-HBs antibodies ≥ 10 mIU/mL (N=64). Ninety percent of infants who received Hib simultaneously with *Infanrix* achieved anti-PPV antibodies ≥ 1 mcg/mL (N=72), and 96% to 100% of infants who received OPV simultaneously with *Infanrix* showed protective neutralizing antibody to poliovirus types 1, 2 and 3 (N=60-61).¹⁶

In the Italian efficacy trial, 92% of infants received hepatitis B vaccine with the first and second dose of *Infanrix*. Ninety-four percent of infants received OPV with the first and second dose of *Infanrix*.¹³

INDICATIONS AND USAGE

Infanrix is indicated for active immunization against diphtheria, tetanus and pertussis (whooping cough) in infants and children 6 weeks to 7 years of age (prior to seventh birthday). Because of the substantial risks of complications from pertussis disease, completion of a primary series of vaccine early in life is strongly recommended.¹ Individuals 7 years of age or older should not receive this vaccine. In such individuals, Tetanus and Diphtheria Toxoids Adsorbed For Adult Use (Td) is preferable to use of either tetanus or diphtheria toxoids alone.

Children who have recovered from culture-confirmed pertussis need not receive further doses of a pertussis-containing vaccine, but should receive additional doses of Diphtheria and Tetanus Toxoids Adsorbed (DT) for pediatric use to complete the series in accordance with ACIP recommendations.¹

In instances where the pertussis vaccine component is contraindicated, Diphtheria and Tetanus Toxoids Adsorbed (DT) for pediatric use may be substituted for each of the remaining doses (see CONTRAINDICATIONS).

The decision to administer or delay vaccination because of a current or recent febrile illness depends on the severity of symptoms and on the etiology of the disease. All vaccines can be administered to persons with minor illness such as diarrhea, mild upper respiratory infections with or without low-grade fever or other low-grade febrile illness.^{1,17}

Where passive protection is required, Tetanus Immune Globulin and/or Diphtheria Antitoxin may also be administered at separate sites.^{1,17}

As with any vaccine, *Infanrix* may not protect 100% of individuals receiving the vaccine.

This product is not recommended for treatment of actual infections.

CONTRAINDICATIONS

Hypersensitivity to any component of the vaccine is a contraindication (see DESCRIPTION).

It is a contraindication to use this vaccine after an immediate anaphylactic reaction temporarily associated with a previous dose. Because of the uncertainty as to which component of the vaccine might be responsible, no further vaccination with diphtheria, tetanus or pertussis should be given. Alternatively, because of the importance of tetanus vaccination, such individuals may be referred to an allergist for evaluation.¹

Immunization should be deferred during the course of a moderate or severe febrile illness or acute infection (see PRECAUTIONS).^{1,17,18}

Elective immunization should be deferred during an outbreak of poliomyelitis.¹⁹

Safety data on the use of *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) in children for whom whole-cell pertussis vaccine is contraindicated are not available. Until such data are available, it would be prudent to consider Advisory Committee on Immunization Practices (ACIP) and American Academy of Pediatrics (AAP) contraindications to whole-cell DTP vaccine as contraindications to *Infanrix*.^{18,20}

The ACIP states that "if any of the following events occur in temporal relationship to the administration of DTP, further vaccination with DTP is contraindicated":

1. An immediate anaphylactic reaction.
2. Encephalopathy (not due to another identifiable cause). This is defined as an acute, severe central nervous system disorder occurring within 7 days following vaccination (with whole-cell DTP or acellular DTP), and generally consisting of major alterations in consciousness, unresponsiveness, generalized or focal seizures that persist more than a few hours, with failure to recover within 24 hours. Even though causation by DTP vaccine cannot be established, no subsequent doses of pertussis vaccine should be given.

WARNINGS

If any of the following events occur in temporal relation to receipt of whole-cell DTP or acellular DTP vaccine, the decision to give subsequent doses of vaccine containing the pertussis component should be carefully considered. There may be circumstances, such as high incidence of pertussis, in which the potential benefits outweigh possible risks, particularly since these events have not been proven to cause permanent sequelae.¹⁸ The following events were previously considered contraindications and are now considered precautions by the ACIP:

- Temperature of $\geq 40.5^{\circ}\text{C}$ (105°F) within 48 hours not due to another identifiable cause
- Collapse or shock-like state (hypotonic-hyporesponsive episode) within 48 hours
- Persistent, inconsolable crying lasting 23 hours, occurring within 48 hours
- Convulsions with or without fever occurring within 3 days

In the Italian efficacy trial, the incidence of temperature $\geq 104^{\circ}\text{F}$, crying for 3 hours or more and seizures within 48 hours of vaccination was less than that following administration of whole-cell DTP vaccine manufactured by Connaught Laboratories, Inc. No hypotonic-hyporesponsive episodes were reported after administration of *Infanrix* in this trial¹³ (see ADVERSE EVENTS—Table 7).

A committee of the Institute of Medicine (IOM) has concluded that evidence is consistent with a causal relationship between whole-cell DTP vaccine and acute neurologic illness, and under special circumstances, between whole-cell DTP vaccine and chronic neurologic disease in the context of the National Childhood Encephalopathy Study (NCES) report.^{21,22} However, the IOM committee concluded that the evidence was insufficient to indicate whether or not whole-cell DTP vaccine increased the overall risk of chronic neurologic disease.²² While acute encephalopathy and permanent neurologic damage have not been reported in temporal association after administration of *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed), the data at this time are insufficient to rule this out.

The ACIP and the AAP recognize certain circumstances in which children with stable central nervous system disorders, such as well-controlled seizures or satisfactorily explained single seizures, may receive pertussis vaccine.

(continued)

Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) continued

The decision to administer a pertussis-containing vaccine to such children must be made by the physician on an individual basis, with consideration of all relevant factors, and assessment of potential risks and benefits for that individual. ACIP and AAP have issued guidelines for such children.^{1,18,20} The parent or guardian should be advised of the potential increased risk involved (see information for the Patient).

Studies suggest that, when given whole-cell DTP vaccine, infants and children with a history of convulsions in first-degree family members (i.e., siblings and parents) have a 2.4-fold increased risk for neurologic events compared with those without such histories.²³ However, the ACIP has concluded that a history of convulsions or other central nervous system disorders in parents or siblings is not a contraindication to pertussis vaccine and that children with such family histories should receive pertussis vaccine according to the recommended schedule.^{1,17,18,24}

For children at higher risk for seizures than the general population, it may be prudent to extend the ACIP and AAP recommendations for whole-cell DTP vaccine to *Infanrix* that acetaminophen be administered at age-appropriate doses at the time of DTP vaccination and every 4 to 6 hours for 24 hours.^{1,18,20}

Infanrix should not be given to infants or children with any coagulation disorder, including thrombocytopenia, that would contraindicate intramuscular injection unless the potential benefit clearly outweighs the risk of administration.

PRECAUTIONS

Although a moderate or severe febrile illness is sufficient reason to postpone vaccination, minor illnesses such as mild upper respiratory infections with or without low-grade fever are not contraindications.^{1,18}

Before the injection of any biological, the physician should take all reasonable precautions to prevent allergic or other adverse reactions, including understanding the use of the biological concerned, and the nature of the side effects and adverse reactions that may follow its use.

Prior to immunization, the patient's medical history should be reviewed. The physician should review the patient's immunization history for possible vaccine sensitivity, previous vaccination-related adverse reactions and occurrence of any adverse-event-related symptoms and/or signs, in order to determine the existence of any contraindication to immunization with *Infanrix* and to allow an assessment of benefits and risks. Epinephrine injection (1:1000) and other appropriate agents used for the control of immediate allergic reactions must be immediately available should an acute anaphylactic reaction occur.

A separate sterile syringe and needle or a sterile disposable unit should be used for each individual patient to prevent transmission of hepatitis or other infectious agents from one person to another. Needles should be disposed of properly and should not be recycled.

Special care should be taken to prevent injection into a blood vessel.

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is not contraindicated for use in individuals with HIV infection.^{12,25}

As with any vaccine, if administered to immunosuppressed persons, including individuals receiving immunosuppressive therapy, the expected immune response may not be obtained.²⁵

Information for the Patient

Parents or guardians should be informed of the potential benefits and risks of the vaccine, and of the importance of completing the immunization series. It is important when a child returns for the next dose in a series that the parent/guardian be questioned concerning occurrence of any symptoms and/or signs of an adverse reaction after a previous dose of the same vaccine. The physician should inform the parents or guardians about the potential for adverse reactions that have been temporally associated with administration of *Infanrix* or other pertussis-containing vaccines. The parents or guardians of infants and children with a family history of convulsions should be advised of the potential increased risk of seizures following DTP vaccination. In particular, they should be told, before the child is vaccinated, to seek immediate medical evaluation in the unlikely event of a seizure.²⁴ The adult accompanying the recipient should be told to report severe or unusual adverse reactions to the physician or clinic where the vaccine was administered.

The parent or guardian should be given the Vaccine Information Materials, which are required by the National Childhood Vaccine Injury Act of 1986 to be given prior to immunization.

The U.S. Department of Health and Human Services has established a Vaccine Adverse Event Reporting System (VAERS) to accept all reports of suspected adverse events after the administration of any vaccine, including but not limited to the reporting of events required by the National Childhood Vaccine Injury Act of 1986.²⁶ The VAERS toll-free number is 1-800-822-7967.

Drug Interactions

For information regarding simultaneous administration with other vaccines, refer to DOSAGE AND ADMINISTRATION and CLINICAL PHARMACOLOGY.

As with other intramuscular injections, *Infanrix* should not be given to infants or children on anticoagulant therapy unless the potential benefit clearly outweighs the risk of administration (see WARNINGS).

Immunosuppressive therapies, including irradiation, antimetabolites, alkylating agents, cytotoxic drugs and corticosteroids (used in greater than physiologic doses), may reduce the immune response to vaccines. Although no specific data from studies with pertussis vaccine under these conditions are available, if immunosuppressive therapy will be discontinued shortly, it would be reasonable to defer immunization until the patient has been off therapy for 1 month; otherwise, the patient should be vaccinated while still on therapy (see PRECAUTIONS).¹ If *Infanrix* is administered to a person receiving immunosuppressive therapy, or a recent injection of immune globulin, or who has an immunodeficiency disorder, an adequate immunologic response may not be obtained.

Tetanus Immune Globulin or Diphtheria Antitoxin, if used, should be given at a separate site, with a separate needle and syringe.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Infanrix has not been evaluated for carcinogenic or mutagenic potential, or for impairment of fertility.

Pregnancy, Pregnancy Category C

Animal reproduction studies have not been conducted with *Infanrix*. It is not known whether *Infanrix* can cause fetal harm when administered to a pregnant woman or if *Infanrix* can affect reproductive capacity. *Infanrix* is not recommended for use in a pregnant woman. *Infanrix* is not recommended for persons 7 years of age or older.

Pediatric Use

Safety and effectiveness of *Infanrix* in infants below the age of 6 weeks have not been established (see DOSAGE AND ADMINISTRATION). *Infanrix* is not recommended for individuals 7 years of age or older. Tetanus and Diphtheria Adsorbed For Adult Use (Td) is to be used in individuals 7 years of age or older.

ADVERSE REACTIONS

A total of 92,502 doses of *Infanrix* has been administered in clinical studies. In these studies, 28,479 infants have received *Infanrix* as a three-dose primary series, 5,830 children have received *Infanrix* as a fourth dose following three doses of *Infanrix*, and 22 children have received *Infanrix* as a fifth dose following four doses of *Infanrix*. In addition, 439 children and 169 children have received *Infanrix* as a fourth or fifth dose following three or four doses of whole-cell DTP vaccine, respectively. In comparative studies, *Infanrix* has been shown to be followed by fewer of the local and systemic adverse reactions commonly associated with whole-cell DTP vaccination. However, studies have shown that the rate of erythema, swelling and fever increased with successive doses of *Infanrix*.

In the double-blind, randomized comparative trial in Italy, safety data in a three-dose primary series are available for 4,696 infants who received at least one dose of *Infanrix* and 4,678 infants who received at least one dose of U.S.-licensed whole-cell DTP vaccine manufactured by Connaught Laboratories, Inc.^{13,15} Data were actively collected by parents using standardized diaries for eight consecutive evenings after each vaccine dose with follow-up telephone calls made by nurses after the eighth day. Table 1 lists adverse events reported during the three days after each dose. All common solicited adverse events were less frequent following vaccination with *Infanrix* as compared to whole-cell DTP after each one of the three doses.

Table 1.¹³ Adverse Events (%) Occurring Within the 3 Days Following Vaccination of Italian Infants with Either *Infanrix* or Whole-Cell DTP at 2, 4 and 6 Months of Age

	<i>Infanrix</i>			Whole-Cell DTP Vaccine		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of infants	4,696	4,560	4,505	4,678	4,474	4,368
Local						
Redness	4.8	8.6	16.0	27.1	24.2	28.0
≥2.4 cm	1.0	1.3	3.5	12.4	7.3	7.7
Swelling	5.2	8.2	14.5	28.9	23.5	25.8
≥2.4 cm	0.7	1.2	2.9	13.1	7.4	8.0
Tenderness	4.7	4.0	5.2	36.0	26.8	25.9
Systemic						
Fever						
≥100.4°F*	7.1	7.9	9.0	46.8	36.1	39.8

Irritability	36.3	34.9	28.8	57.2	50.1	47.2
Drowsiness	34.9	18.8	11.4	54.0	34.1	23.0
Loss of Appetite	16.5	13.9	11.5	31.2	22.8	19.1
Vomiting	5.8 [†]	4.1 [†]	3.3	6.7	4.7	4.8
Crying						
≥1 Hour	3.9	3.3	2.2	17.3	11.1	8.2

* Rectal temperatures.

[†] For the comparison of *Infanrix* and whole-cell DTP vaccine, all adverse events reached statistical significance (p<0.001) at all doses except vomiting at doses 1 and 2, which was not statistically significant at p<0.05.

A similar reduction in adverse events was seen in a randomized, double-blind, comparative trial conducted in the U.S. when *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) was compared to two U.S.-licensed whole-cell DTP vaccines. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at days 1, 4 and 8 by blinded study personnel. Table 2 summarizes the frequency of adverse events within 3 days of the three primary immunizing doses. The incidence of redness, swelling, pain, fever (rectal temperature >101°F), fussiness, drowsiness and poor appetite, were lower following *Infanrix* than following either whole-cell DTP vaccine.

Table 2.²⁷ Adverse Events (%) Occurring Within the 3 Days Following Vaccination of U.S. Infants with Either *Infanrix* or Whole-Cell DTP at 2, 4 and 6 Months of Age

	<i>Infanrix</i>			Whole-Cell DTP Vaccine-Lederle			Whole-Cell DTP Vaccine-Connaught		
	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
No. of infants	407	402	395	74	73	73	76	75	74
Local									
Redness*	10.6	19.4	25.8	28.4	42.5	39.7	35.5	50.7	50.0
Swelling	7.4 [†]	12.2 [†]	17.5 [†]	23.0 [†]	26.0 [†]	27.4	30.3 [†]	37.3 [†]	31.1 [†]
Pain* [‡]	2.7	2.0	1.5	17.6	15.1	9.6	38.2	17.3	14.9
Systemic									
Fever									
>101°F§	0.5 [†]	0.7 [†]	5.1	12.2 [†]	8.2 [†]	6.8	14.5 [†]	18.7 [†]	8.1
Fussiness**	3.9 [†]	3.5 [†]	4.1	25.7 [†]	13.7 [†]	6.8	21.1 [†]	16.0 [†]	8.1
Drowsiness	26.3 [†]	16.4 [†]	12.9 [†]	51.4 [†]	34.2 [†]	23.3 [†]	52.6 [†]	28.0 [†]	18.9
Poor Appetite	8.1 [†]	7.7	6.6	31.1 [†]	15.1	9.6	19.7 [†]	14.7	9.5
Vomiting	6.6	3.7	3.8	8.1	4.1	2.7	7.9	2.7	2.7

* Moderate or severe = cried or protested to touch or cried when limb moved.

** Moderate or severe = prolonged crying and refusal to play or persistent crying that could not be comforted.

[†] Rectal temperatures.

[‡] p<0.05 for the comparison of *Infanrix* and both whole-cell DTP vaccines.

[§] p<0.05 for the comparison of *Infanrix* and whole-cell DTP vaccine-Lederle.

[¶] p<0.05 for the comparison of *Infanrix* and whole-cell DTP vaccine-Connaught.

The frequencies of adverse reactions following each dose in children who received *Infanrix* at 2, 4 and 6 months of age in a U.S. NIH-sponsored trial are shown in Table 3. Of the 120 infants who received the three-dose primary series, a subset of 76 received a fourth dose of *Infanrix* at 15 to 20 months of age. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at day 3 by blinded study personnel.

Table 3.^{15,28} Adverse Events (%) Occurring Within the 3 Days Following Vaccination with *Infanrix* in U.S. Infants and Children in Which All Doses Were *Infanrix*

Event	Primary (N = 120 infants)			Booster (N = 76 children)
	Dose 1 (2 months)	Dose 2 (4 months)	Dose 3 (6 months)	Dose 4 (15 to 20 months)
Local				
Redness	16.6	15.4	26.3	39.5
Swelling	12.5	15.4	21.0	32.9
Pain*	5.0	5.1	0.9	10.5
Systemic				
Fever (>101°F)†	0.0	0.9	3.5	6.6
Anorexia	7.5	6.0	9.6	11.8
Vomiting	5.8	6.8	3.5	2.6
Drowsiness	37.5	19.7	13.2	6.6
Fussiness‡	3.3	7.7	8.8	9.2

* Moderate or severe = cried or protested to touch or cried when limb moved.

† Rectal temperatures for primary series; oral temperatures for booster.

‡ Moderate or severe = prolonged crying and refusal to play or persistent crying that could not be comforted.

Of 22,505 children who had previously received three doses of *Infanrix* at 3, 4 and 5 months of age in the large German safety study, 5,361 received a fourth dose at 10 to 36 (mean 20) months of age. Standardized diaries were available on 2,457 children receiving the primary series and 1,809 children receiving the fourth dose. Local and systemic reaction rates within 3 days of vaccination for each dose are reported in Table 4. In this study, the rate of erythema, swelling, pain and fever increased with successive doses of *Infanrix*.

In another study conducted in Germany, which was double-blind and randomized, additional safety data are available from 13- to 27-month-old children who received *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) or whole-cell DTP vaccine, manufactured by Behringwerke, A.G., as a fourth dose. These children had previously received three doses of the same vaccine. The rates of adverse events, which were actively solicited using standardized diaries, are presented in Table 5. The incidence of redness, swelling, severe swelling (greater than 2 cm), pain, fever, severe fever (rectal temperature >103.1°F), restlessness, loss of appetite, vomiting, drowsiness and unusual crying was lower following vaccination with *Infanrix* compared to whole-cell DTP vaccine.

Table 4.¹⁵ Adverse Events (%) Occurring Within the 3 Days Following Vaccination with *Infanrix* in German Infants and Children in Which All Doses Were *Infanrix*

Event	Primary (N=2,457 infants)			Booster (N=1,809 children)*
	Dose 1 (3 months)	Dose 2 (4 months)	Dose 3 (5 months)	Dose 4 (10 to 36 months)†
Local				
Redness	8.9	23.6	26.6	45.9
Redness >2 cm	0.0	0.5	1.3	13.8
Swelling	3.9	14.1	18.5	35.4
Swelling >2 cm	0.0	0.3	1.3	11.4
Pain	2.0	2.6	3.7	26.3
Systemic				
Fever				
≥100.4°F‡	6.3	8.3	13.3	26.4
>103.1°F‡	0.0	0.1	0.1	1.1
Loss of Appetite	8.0	7.4	6.5	11.6
Vomiting	4.3	3.9	3.4	2.9
Restlessness	10.3	9.5	8.6	15.9
Unusual Crying	3.9	4.3	4.1	6.4
Diarrhea	6.0	4.9	4.0	11.0

* May not be same children as in primary series.

† Mean = 20 months.

‡ Rectal temperatures.

Table 5.¹⁴ Adverse Events (%) Occurring Within the 3 Days Following Vaccination with *Infanrix* or Whole-Cell DTP (Fourth Dose) in German Children Who Had Received Three Previous Doses of the Same Vaccine

Event	<i>Infanrix</i> After <i>Infanrix</i> Primary (N=268)	Whole-Cell DTP Vaccine After Whole-Cell DTP Vaccine Primary (N=92)
Local		
Redness	32.8	43.5
Redness >2 cm	4.5	3.3
Swelling	22.4	31.5
Swelling >2 cm	3.0	7.6
Pain [†]	15.7	55.4
Systemic		
Fever (≥100.4°F) [‡]	26.9	64.1
Fever (>103.1°F) [‡]	0.4	4.3
Restlessness [§]	12.3	32.6
Loss of Appetite [¶]	10.8	43.5
Vomiting	3.4	7.6
Drowsiness ^{**}	10.4	31.5
Unusual Crying ^{**}	7.8	33.7

* p<0.0001.
[†] Rectal temperatures.
[‡] p<0.05.

Cases of edematous swelling, generally beginning within 48 hours of vaccination and resolving spontaneously over an average of 4 days without sequelae, have been reported with *Infanrix*.¹⁵ In the German study in which 5,361 children received a fourth dose of *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) after three doses of the same vaccine, swelling of the injected thigh was reported spontaneously in 62 vaccinees (1.2%). This swelling was associated with pain upon digital pressure in 53% of cases, with rectal temperature ≥100.4°F in 45% of cases, and with injection site redness in 71% of cases (redness of the entire thigh was reported in 17% of such cases). The mean difference in the circumference of the thighs in those subjects in whom this was measured (N=17) was 2.2 cm (range: 0.5 to 5 cm), in 1,809 children for whom standardized diaries were available, edematous swelling was observed in 2.5% of vaccinees.

In clinical studies of *Infanrix* to date, edematous swelling has been seen only with *Infanrix* as a fourth dose in *Infanrix*-primed individuals. In other countries where *Infanrix* has been licensed, limb swelling has been reported rarely following administration of *Infanrix* at any dose, including the primary series. Edematous swelling has also been reported following administration of other acellular DTP vaccines,²⁰ acellular pertussis vaccine alone (without DT),²¹ whole-cell DTP vaccine²¹ and other vaccines.²²

Table 6 lists the frequency of adverse events in U.S. children who received *Infanrix* (N=110) or U.S.-licensed whole-cell DTP vaccine (N=55) manufactured by Lederle Laboratories at 15 to 20 months of age²³ and in U.S. children who received *Infanrix* (N=115) or U.S.-licensed whole-cell DTP vaccine (N=57) manufactured by Lederle Laboratories at 4 to 6 years of age.²⁴ All children had previously received three or four doses of whole-cell DTP vaccine at approximately 2, 4, 6 and 15-18 months of age. Adverse events were actively solicited using standardized diaries with follow-up telephone calls made at days 1, 4 and 8 by blinded study personnel. Significantly fewer solicited local and general adverse events were reported following *Infanrix* than following whole-cell DTP vaccine when administered as the fourth or fifth dose in those previously primed with three or four doses of whole-cell DTP vaccine.

Table 6.^{23,24} Adverse Events (%) Occurring Within the 3 Days Following Vaccination with *Infanrix* Administered at 15 to 20 Months and 4 to 6 Years of Age in U.S. Children Who Had Previously Received Three or Four Doses of Whole-Cell DTP Vaccine

Event	15 to 20 months Three Previous Doses of Whole-Cell DTP Vaccine		4 to 6 years Four Previous Doses of Whole-Cell DTP Vaccine	
	<i>Infanrix</i> (N=110)	Whole-Cell DTP Vaccine (N=55)	<i>Infanrix</i> (N=115)	Whole-Cell DTP Vaccine (N=57)
Local				
Redness*	23	45	19	40
Redness [†] >10 mm	5	31	7	26
Swelling	14	24	15*	33*
Swelling [†] >10 mm	7	15	8	18
Pain [‡]	5	38	12	40
Systemic				
Fever [§]				
≥99.4°F [§]	25	42	23	47
Fever [¶] >100.5°F [¶]	2	20	1	12
Fussiness	34 [¶]	69 [¶]	20	30
Drowsiness	9*	24*	11	18
Poor Appetite ^{**}	9	20	6	16
Vomiting	2	0	1	4

* p<0.05.
[†] p<0.0001.
[‡] Oral temperatures.
[§] Moderate or severe = cried or protested to touch or cried when arm moved.

Severe adverse events reported from the double-blind, randomized comparative Italian study involving 4,896 children administered *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) or 4,678 children administered whole-cell DTP vaccine (manufactured by Connaught Laboratories, Inc.) as a three-dose primary series are shown in Table 7. The incidence of rectal temperature ≥104°F, hypotonic-hyporesponsive episodes and persistent crying ≥3 hours following administration of *Infanrix* was significantly less than that following administration of whole-cell DTP vaccine.¹⁵ Hospitalization rates and death rates within 7 days of vaccination were similar between *Infanrix* and DT vaccine recipients.¹⁵

Table 7.¹⁵ Severe Adverse Events Occurring Within 48 Hours Following Vaccination with *Infanrix* or Whole-Cell DTP in Italian Infants at 2, 4 or 6 Months of Age

Event	<i>Infanrix</i> (N=13,761 doses)		Whole-Cell DTP Vaccine (N=13,520 Doses)	
	Number	Rate/ 1,000 Doses	Number	Rate/ 1,000 Doses
Fever ≥104°F [†]	5	0.36	32	2.4
Hypotonic- Hyporesponsive Episode [‡]	0	0	9	0.67
Persistent crying ≥3 hours [§]	6	0.44	54	4.0
Seizures [¶]	1 [¶]	0.07	3 [¶]	0.22

* p<0.001.
[†] Rectal temperatures.
[‡] p = 0.002.
[§] Maximum rectal temperature within 72 hours of vaccination = 103.1°F.
[¶] Maximum rectal temperature within 72 hours of vaccination = 99.5°F, 101.3°F and 102.2°F.
^{**} Not statistically significant at p<0.05.

In the large German safety trial that enrolled 22,505 infants (66,867 doses of *Infanrix* administered as a three-dose primary series), all subjects were monitored for unsolicited adverse events that occurred within 28 days following vaccination using report cards. In a subset of subjects (N=2,457), these cards were standardized diaries which solicited specific adverse events that occurred within 8 days of each vaccination in addition to unsolicited adverse events which occurred throughout the course of the entire trial (from study enrollment until approximately 30 days follow-

ing the third vaccination). Cards from the whole cohort were returned at subsequent visits and were supplemented by spontaneous reporting by parents and a medical history after the first and second doses of vaccine. In the subset of 2,457, adverse events following the third dose of vaccine were reported via standardized diaries and spontaneous reporting at a follow-up visit. Adverse events in the remainder of the cohort were reported via report cards which were returned by mail approximately 28 days after the third dose of vaccine. Adverse events (rates per 1,000 doses) occurring within 7 days including those events deemed by investigators as related as well as those felt to be unrelated to vaccination included: unusual crying (0.09), febrile seizure (0.0), afebrile seizure (0.13) and hypotonic-hyporesponsive episodes (0.01).

Rates of serious adverse experiences that are less common than those reported in the German safety trial are not known at this time.

In clinical trials involving more than 29,000 infants and children, 14 deaths in *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) recipients were reported. Causes of deaths included nine cases of Sudden Infant Death Syndrome (SIDS) and one of each of the following: meal aspiration, hepatoblastoma, neuroblastoma, invasive bacterial infection and sudden death in a child greater than 1 year of age. None of these events was determined to be vaccine-related. The rate of SIDS observed in the large German safety study was 0.3/1000 vaccinated infants. The rate of SIDS in the Italian efficacy trial was 0.4/1000 *Infanrix*-vaccinated infants. The reported rate of SIDS in the U.S. from 1985 to 1991 was 1.5/1000 live births.²⁵ By chance alone, some cases of SIDS can be expected to follow receipt of whole-cell DTP or acellular DTP vaccine.¹⁸

Rarely, an anaphylactic reaction (i.e., hives, swelling of the mouth, difficulty breathing, hypotension, shock) has been reported after receiving preparations containing diphtheria, tetanus and/or pertussis antigens.^{1,18} Arthus-type hypersensitivity reactions, characterized by severe local reactions, may follow receipt of tetanus toxoid. A few cases of peripheral mono-neuropathy have been reported following tetanus toxoid administration, although the IOM concluded that the evidence was inadequate to accept or reject a causal relationship.²⁶

A review by the IOM found evidence for a causal relationship between receipt of tetanus toxoid and both brachial neuritis and Guillain-Barré Syndrome.²⁶

Additional Adverse Reactions Evaluated in Conjunction with Whole-Cell DTP Vaccination
 Whole-cell DTP vaccine has been associated with acute encephalopathy.²⁷ In the National Childhood Encephalopathy Study (NCES), a large, case-control study in England, children 2 to 35 months of age with serious, acute neurologic disorders, such as encephalopathy or complicated convulsions(s), were more likely to have received DTP vaccine in the 7 days preceding onset than their age-matched controls. Among children presumed to be neurologically normal before entering the study, the relative risk (estimated by odds ratio) of a neurologic illness occurring within the 7-day period following receipt of DTP dose, compared to children not receiving DTP vaccine in the 7-day period before onset of their illness, was 3.3 (p<0.001). The attributable risk for all neurologic events was estimated to be 1:140,000 doses of DTP vaccine administered. In this study, a causal relationship between receipt of DTP vaccine and permanent neurologic injury was suggested.^{1,37,40}

A 10-year follow-up to the NCES demonstrated that children who experience a serious acute neurologic illness following whole-cell DTP vaccine are at increased risk for chronic nervous system dysfunction or death.⁴¹ However, the IOM concluded that the results were insufficient to determine whether DTP vaccine increases the overall risk for chronic nervous system dysfunction in children.^{18,22}

Subsequent studies have failed to provide evidence in support of a causal relationship between DTP vaccination and either serious acute neurologic illness or permanent neurologic injury.⁴²⁻⁴⁵ The ACIP and AAP continue to recommend the use of DTP vaccine.

Among a subset of children who were participating in the NCES and who had infantile spasms, both DT and DT vaccine appeared either to precipitate early manifestations of the condition or to lead to its identification by parents.⁴⁶ IOM reviewed this and other studies and concluded that neither vaccine causes the illness.^{18,27,45,47} The incidence of onset of infantile spasms increases at 3 to 9 months of age, the time period in which the second and third doses of DTP vaccine are generally given. Therefore, some cases of infantile spasms can be expected to be temporally associated with receipt of whole-cell DTP or acellular DTP vaccine by chance alone.

SIDS has occurred in infants following administration of whole-cell DTP and acellular DTP vaccine. Large case-control studies of SIDS in the United States have shown that SIDS was not causally related to receipt of DTP vaccine.^{48,49} It should be recognized that the first three primary immunizing doses of DTP vaccine are usually administered to infants 2 to 6 months old and that approximately 85% of SIDS cases occur between the ages of 1 and 6 months, with the peak incidence occurring at 6 weeks to 4 months of age. By chance alone, some cases of SIDS can be expected to be temporally related to recent receipt of whole-cell DTP or acellular DTP vaccine. A review by the committee of the IOM concluded that available evidence did not indicate a causal relation between DTP vaccine and SIDS.^{18,21}

A bulging fontanelle associated with increased intracranial pressure, which occurred within 24 hours following DTP immunization, has been reported, although a causal relationship has not been established.^{50,52}

As with any vaccine, there is the possibility that broad use of *Infanrix* (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) could reveal adverse reactions not observed in clinical trials.

Reporting Adverse Events

The National Childhood Vaccine Injury Act requires that the manufacturer and lot number of the vaccine administered be recorded by the healthcare provider in the vaccine recipient's permanent medical record, along with the date of administration of the vaccine and the name, address and title of the person administering the vaccine.⁵³ The Act further requires the healthcare provider to report to the U.S. Department of Health and Human Services via VAERS the occurrence following immunization of any event set forth in the Vaccine Injury Table including: anaphylaxis or anaphylactic shock within 4 hours, encephalopathy or encephalitis within 72 hours, or any sequelae thereof (including death).^{53,54} In addition, any event considered a contraindication to further doses should be reported.

DOSSAGE AND ADMINISTRATION

Preparation for Administration

Shake the vial well before withdrawal and use. The vaccine is ready to use without reconstitution. Parenteral drug products should be inspected visually for particulate matter or discoloration prior to administration, whenever solution and container permit. With thorough agitation, *Infanrix* is a homogeneous white turbid suspension. Discard if it appears otherwise. Since this product is a suspension containing an adjuvant, shake vigorously to obtain a uniform suspension prior to withdrawal from the vial. DO NOT USE IF RESUSPENSION DOES NOT OCCUR WITH VIGOROUS SHAKING. After removal of the 0.5 mL dose, any vaccine remaining in the vial should be discarded.

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) should be administered by intramuscular injection. The preferred sites are the anterolateral aspects of the thigh or the deltoid muscle of the upper arm. The vaccine should not be injected in the gluteal area or areas where there may be a major nerve trunk. Before injection, the skin at the injection site should be cleaned and prepared with a suitable germicide. After insertion of the needle, aspirate to ensure that the needle has not entered a blood vessel.

Do not administer this product subcutaneously.

Primary Immunization

The primary immunization course for children less than 7 years of age is three doses of 0.5 mL, given intramuscularly, at 4- to 8-week intervals (preferably 8 weeks). The customary age for the first dose is 2 months of age, but it may be given starting at 6 weeks of age and up to the seventh birthday. It is recommended that *Infanrix* be given for all three doses since no interchangeability data on acellular DTP vaccines exist for the primary series. *Infanrix* may be used to complete the primary series in infants who have received one or two doses of whole-cell DTP vaccine. However, the safety and efficacy of *Infanrix* in such infants have not been evaluated.

Booster Immunization

When *Infanrix* is given for the primary series, a fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. At this time, data are insufficient to establish the frequency of adverse events following a fifth dose of *Infanrix* in children who have previously received four doses of *Infanrix*.

If a child has received whole-cell DTP vaccine for one or more doses, *Infanrix* may be given to complete the five-dose series. A fourth dose is recommended at 15 to 20 months of age. The interval between the third and fourth dose should be at least 6 months. Children 4 to 6 years of age (up to the seventh birthday) who received all four doses by the fourth birthday, including one or more doses of whole-cell DTP vaccine, should receive a single dose of *Infanrix* before entering kindergarten or elementary school. This dose is not needed if the fourth dose was given on or after the fourth birthday.

Additional Dosing Information

If any recommended dose of pertussis vaccine cannot be given, DT (For Pediatric Use) should be given as needed to complete the series.

Interruption of the recommended schedule with a delay between doses should not interfere with the final immunity achieved with *Infanrix*. There is no need to start the series over again, regardless of the time elapsed between doses.

The use of reduced volume (fractional doses) is not recommended. The effect of such practices on the frequency of serious adverse events and on protection against disease has not been determined.¹⁷

Preterm infants should be vaccinated according to their chronological age from birth.¹⁷
 For persons 7 years of age or older, Tetanus and Diphtheria Toxoids (Td) for adult use should be given for routine booster immunization against tetanus and diphtheria.

(continued)

Infanrix® (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) continued

Simultaneous Vaccine Administration

In clinical trials, *Infanrix* was routinely administered, at separate sites, concomitantly with one or more of the following vaccines: poliovirus vaccine live oral (OPV), hepatitis B vaccine, and *Haemophilus influenzae* type b vaccine (Hib) (see CLINICAL PHARMACOLOGY).

No data are available on the simultaneous administration of measles, mumps and rubella vaccine (MMR), varicella vaccine or inactivated polio virus (IPV) with *Infanrix*.

When concomitant administration of other vaccines is required, they should be given with different syringes and at different injection sites.

The ACIP encourages routine simultaneous administration of acellular DTP, OPV (or IPV), Hib, MMR and hepatitis B vaccine for children who are at the recommended age to receive these vaccines and for whom no specific contraindications exist at the time of the visit, unless, in the judgment of the provider, complete vaccination of the child will not be compromised by administering vaccines at different visits. Simultaneous administration is particularly important if the child might not return for subsequent vaccinations.¹⁷

STORAGE

Store *Infanrix* between 2° and 8°C (36° and 46°F). Do not freeze. Discard if the vaccine has been frozen. Do not use after expiration date shown on the label.

HOW SUPPLIED

Infanrix (Diphtheria and Tetanus Toxoids and Acellular Pertussis Vaccine Adsorbed) is supplied as a turbid white suspension in vials containing a 0.5 mL single dose, in packages of 10 vials.

NDC 58160-840-11 (package of 10)

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